

=> fil reg

FILE 'REGISTRY' ENTERED AT 16:53:39 ON 09 DEC 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 8 DEC 2003 HIGHEST RN 625077-42-1
DICTIONARY FILE UPDATES: 8 DEC 2003 HIGHEST RN 625077-42-1

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> d ide can tot ll

L1 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2003 ACS on STN
RN 113189-02-9 REGISTRY
CN Blood-coagulation factor VIII, procoagulant (9CI) (CA INDEX NAME)
OTHER NAMES:
CN AHF-A
CN Antihemophilic factor
CN Antihemophilic factor A
CN Antihemophilic globulin
CN Bioclote
CN Blood-coagulation factor VIII
CN Blood-coagulation factor VIIIC
CN Coagulation factor VIIIC
CN **Factor VIII**
CN Koate DVI
CN Monoclote
CN Monoclote-P
MF Unspecified
CI MAN
SR CA
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, CA, CAPLUS,
CBNB, CEN, CIN, DIOGENES, DRUGNL, DRUGPAT, DRUGUPDATES, IPA, MSDS-OHS,
PHAR, PIRA, PROMT, TOXCENTER, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

1700 REFERENCES IN FILE CA (1907 TO DATE)
43 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1702 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:362806
REFERENCE 2: 139:362805
REFERENCE 3: 139:362778
REFERENCE 4: 139:359345
REFERENCE 5: 139:345630

REFERENCE 6: 139:337302

REFERENCE 7: 139:337300

REFERENCE 8: 139:336912

REFERENCE 9: 139:336550

REFERENCE 10: 139:336229

L1 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2003 ACS on STN

RN 109319-16-6 REGISTRY

CN Blood-coagulation factor VIII, von Willebrand's (9CI) (CA INDEX NAME)

OTHER NAMES:

CN Antigens, blood-coagulation factor VIII-related

CN Blood platelet-aggregating factor

CN Blood-coagulation factor VIII

CN Blood-coagulation factor VIII antigen

CN Blood-coagulation factor VIII-related antigen

CN Blood-coagulation factor VIIIR

CN **Factor VIII**

CN Ristocetin cofactor

CN Ristocetin-von Willebrand factor

CN von Willebrand's factor

MF Unspecified

CI MAN

SR CA

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,
CA, CAPLUS, CEN, CIN, DIOGENES, EMBASE, IPA, PIRA, PROMT, TOXCENTER,
USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

3650 REFERENCES IN FILE CA (1907 TO DATE)

74 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

3659 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:364163

REFERENCE 2: 139:363446

REFERENCE 3: 139:362781

REFERENCE 4: 139:362151

REFERENCE 5: 139:362134

REFERENCE 6: 139:361116

REFERENCE 7: 139:359540

REFERENCE 8: 139:349510

REFERENCE 9: 139:349298

REFERENCE 10: 139:349229

L1 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2003 ACS on STN

RN 9001-27-8 REGISTRY

CN Blood-coagulation factor VIII, complex (9CI) (CA INDEX NAME)

OTHER NAMES:

CN AHF

CN AHF-HP

CN AHG
CN Amofil
CN Beriate HS
CN Biostate P
CN Blood-coagulation factor VIII
CN **Factor VIII**
CN Factorate
CN Fanhdi
CN FVIII-THP/SD
CN Haemate HS
CN Haemate P
CN Haemoctin SDH
CN Hemate P
CN Hemofil
CN Hemofil M
CN Humafac
CN Humate P
CN Koate HP
CN Nordiocto
CN Octonativ-M7
CN Profilate
CN Thromboplastinogen
DR 9035-62-5, 114046-09-2
MF Unspecified
CI COM, MAN
LC STN Files: AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA,
CANCERLIT, CAPLUS, CBNB, CEN, CHEMLIST, CIN, DDFU, DIOGENES, DRUGU,
EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH,
PIRA, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
3589 REFERENCES IN FILE CA (1907 TO DATE)
66 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3590 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:358433
REFERENCE 2: 139:357967
REFERENCE 3: 139:349043
REFERENCE 4: 139:347728
REFERENCE 5: 139:345632
REFERENCE 6: 139:345182
REFERENCE 7: 139:345181
REFERENCE 8: 139:341652
REFERENCE 9: 139:333055
REFERENCE 10: 139:318625

=> d his

(FILE 'HOME' ENTERED AT 15:27:10 ON 09 DEC 2003)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 15:32:38 ON 09 DEC 2003

E FACTOR VIII/CN

L1 3 S E3

FILE 'HCAPLUS' ENTERED AT 15:33:16 ON 09 DEC 2003

L2 8289 S L1
L3 3570 S BLOOD() (COAGULAT? OR CLOT?) () FACTOR VIII
L4 4986 S VON WILLEBRAND? FACTOR
L5 3884 S (COAGULAT? OR CLOT?) () FACTOR VIII
L6 6989 S FACTOR VIII
L7 4171 S (COAGULAT? OR CLOT?) () FACTOR VIII#
L8 3750 S BLOOD() (COAGULAT? OR CLOT?) () FACTOR VIII#
L9 5107 S VON() (WILLEBRAND? OR WILLEBRAND S) () FACTOR
L10 331 S BLOOD? FACTOR VIII#
L11 38 S THROMBOPLASTINOGEN?
L12 11515 S L2-L11
E VOORBERG J/AU
L13 44 S E3-E6
E VANDENBRINK/AU
E VANDEN BRINK/AU
E VAN DENBRINK/AU
E VAN DEN BRINK/AU
L14 10 S E20,E21
E DEN BRINK/AU
E DENBRINK/AU
E BRINK/AU
E TURENHOUT E/AU
L15 10 S E4,E5
E STICHTING/PA,CS
E SANQUI/PA,CS
L16 100 S E5,E6
L17 24 S E7-E28
L18 45 S L12 AND L13-L17
SEL DN AN 21
L19 1 S E1-E3 AND L18
L20 2603 S L12 AND ANTIBOD?
L21 1676 S L20 AND (?PROTEIN? OR ?PEPTIDE? OR AMINOACID? OR AMINO ACID?)
L22 3 S L20 AND (PROTEIN? OR PEPTIDE? OR AMINO ACID?)/SC, SX
E PROTEIN/CT
E PROTEIN/CW
L23 579 S L20 AND E3,E7
E PROTEINS/CT
E PROTEIN SEQUENCE/CT
E E11+ALL
L24 156 S L20 AND E2+NT
E E9+ALL
L25 102 S L20 AND E4+NT
E PEPTIDE/CW
L26 138 S L20 AND E3,E4
E POLYPEPTIDE/CW
L27 5 S L20 AND E3,E5
E PEPTIDE/CT
L28 246 S L20 AND E88+NT
E E88+ALL
E POLYPEPTIDE/CT
E E10+ALL
L29 0 S L20 AND E1
L30 417 S L20 AND E2,E3
L31 1700 S L21-L30
E AMINO ACID/CT
L32 124 S L20 AND E42+NT
L33 1709 S L31,L32

L34 239 S L33 AND ?IMMUNOGLOBULIN?
 E IMMUNOGLOBULIN/CT
 E E4+ALL
 L35 513 S E2
 L36 339 S E4
 L37 5501 S E14
 E IMMUNOGLOBULINS/CT
 L38 29558 S E43
 L39 1074 S E72
 L40 81 S E73
 L41 314 S E74
 L42 1833 S E81
 L43 12764 S E83
 L44 1694 S E36
 L45 138 S L33 AND L35-L44
 L46 239 S L34, L45
 L47 153 S L33 AND (IGA OR IGD OR IGG OR IGM OR IGG4)
 L48 110 S L33 AND (IMMUNOGLOBULIN OR IG) () (A OR D OR G OR M OR G4)
 L49 25 S L33 AND (IMMUNOGLOBULIN OR IG) (L) (HEAVY OR LIGHT) (L) CHAIN
 L50 45 S L33 AND (IMMUNOGLOBULIN OR IG) (L) FRAGMENT
 L51 306 S L46-L50
 L52 12 S L33 AND ?SCFV?
 L53 1 S L33 AND (IMMUNOGLOBULIN OR IG) (L) SINGLE(L) CHAIN
 L54 193 S L33 AND FV?
 L55 0 S L33 AND (?SCFVEL? OR ?SCFVIT?)
 L56 0 S L33 AND (?FVEL? OR ?FVIT?)
 L57 0 S L54 AND (EL14 OR 1T2 OR IT2)
 L58 10 S L33 AND VARIABLE REGION
 L59 459 S L51-L58
 L60 2 S L33 AND (DP10 OR DP14 OR DP15 OR DP31 OR DP47 OR DP49 OR DP77
 L61 459 S L59, L60
 L62 49 S L33 AND (IMMUNOGLOBULIN OR IG) (L) (A1 OR A3 OR C1 OR C2 OR M O
 L63 459 S L61, L62
 L64 6 S L33 AND CDR3
 L65 0 S L33 AND CDR 3
 L66 0 S L33 AND CD R3
 L67 0 S L33 AND CD R 3
 L68 459 S L63, L64
 L69 480 S L33 AND (A1 OR M OR B OR A3 OR C1 OR C2)
 L70 752 S L68, L69
 L71 12 S L18 AND L70
 L72 3 S L19, L71 AND (PD<=19980508 OR PRD<=19980508 OR AD<=19980508)
 L73 427 S L70 AND (PD<=19980508 OR PRD<=19980508 OR AD<=19980508)
 E HEMOPHIL/CT
 L74 1076 S E5
 E E4+ALL
 L75 2792 S E5
 E E7+ALL
 L76 860 S E5
 L77 40 S E5/BI OR E6/BI OR E7/BI
 L78 3682 S E8/BI
 L79 13425 S HEMOPHILI? OR HAEMOPHIL?
 L80 100 S L73 AND L74-L79
 L81 55 S L80 AND (HEMOPHILI? OR HAEMOPHIL?) () A
 L82 45 S L80 NOT L81
 SEL DN AN 1 2 8 11 19 42
 L83 6 S L82 AND E1-E18
 SEL DN AN 1 2 4 5 12 17 22 48 50 L81
 L84 9 S L81 AND E19-E45
 L85 17 S L72, L83, L84 AND L2-L84
 L86 16 S L85 AND (IG OR IGA IR IGD OR IGG OR IGM OR IGG4 OR A1 OR A2 O
 L87 13 S L85 AND (?SCFV? OR SC OR FV? OR IMMUNOGLOBULIN? OR CD43)
 L88 17 S L85-L87

L89 8 S L12 AND CDR3
L90 0 S L12 AND CDR 3
L91 0 S L12 AND CD R 3
L92 0 S L12 AND CD R3
L93 15 S L12 AND COMPLEMENT?(L) DETERMIN?(L) REGION
L94 0 S L12 AND COMPLEMENT?(L) DETERMIN?(L) R3
L95 20 S L89,L93
L96 14 S L95 AND (PD<=19980508 OR PRD<=19980508 OR AD<=19980508)
L97 3 S L12 AND CDR
L98 3 S L97 AND (PD<=19980508 OR PRD<=19980508 OR AD<=19980508)
L99 14 S L96,L98
SEL DN AN 2 7 8
L100 3 S L99 AND E46-E54
L101 19 S L88,L100 AND L2-L100

FILE 'REGISTRY' ENTERED AT 16:53:39 ON 09 DEC 2003

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 16:53:46 ON 09 DEC 2003

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 9 Dec 2003 VOL 139 ISS 24

FILE LAST UPDATED: 8 Dec 2003 (20031208/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all tot l101

L101 ANSWER 1 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 2002:429466 HCAPLUS

DN 137:19402

ED Entered STN: 07 Jun 2002

TI Antigenic **polypeptide** sequences of **Factor VIII**
, and fragments and/or epitopes of these sequences for use in treatment
and diagnosis of **hemophilia**

IN Laub, Ruth; Di Giambattista, Mario

PA Belg.

SO U.S. Pat. Appl. Publ., 25 pp., Cont.-in-part of U. S. Ser. No. 765,837.
CODEN: USXXCO

DT Patent

LA English

IC ICM C07K005-00

ICS C07K007-00; C07K016-00; C07K017-00; A61K038-00; A61K038-04;
C07K001-00; C07K014-00; A61K035-14; G01N033-53; C12P021-08

NCL 435007100

CC 15-8 (Immunochemistry)

Section cross-reference(s): 14

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002068303	A1	20020606	US 2001-853080	20010509 <--
	BE 1008491	A3	19960507	BE 1994-666	19940714 <--
	WO 9602572	A2	19960201	WO 1995-BE68	19950714 <--
	WO 9602572	A3	19970213		
	W: CA, JP, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 2003147900	A1	20030807	US 1999-765837	19990907 <--
	WO 2002090542	A2	20021114	WO 2002-BE70	20020506
	W: CA, JP				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
PRAI	BE 1994-666	A	19940714 <--		
	WO 1995-BE68	W	19950714 <--		
	US 1999-765837	A2	19990907		
	US 2001-853080	A	20010509		
AB	The present invention is related to the antigenic polypeptide sequence of Factor VIII . The antigenic epitopes of Factor VIII are used in treatment and diagnosis of hemophilia . Inhibitors of Factor VIII (i.e. antibodies) can be removed from patient serum using the antigenic epitopes bound to a chromatog. column and the serum can be reinjected to the patient.				
ST	hemophilia therapy diagnosis factor VIII epitope antibody				
IT	Hemophilia (A; epitopes of factor VIII for treatment and diagnosis of hemophilia)				
IT	Immunoglobulins RL: ADV (Adverse effect, including toxicity); DGN (Diagnostic use); REM (Removal or disposal); BIOL (Biological study); PROC (Process); USES (Uses) (G2; epitopes of factor VIII for treatment and diagnosis of hemophilia)				
IT	Immunoglobulins RL: ADV (Adverse effect, including toxicity); DGN (Diagnostic use); REM (Removal or disposal); BIOL (Biological study); PROC (Process); USES (Uses) (G4; epitopes of factor VIII for treatment and diagnosis of hemophilia)				
IT	Immunoglobulins RL: ADV (Adverse effect, including toxicity); DGN (Diagnostic use); REM (Removal or disposal); BIOL (Biological study); PROC (Process); USES (Uses) (G; epitopes of factor VIII for treatment and diagnosis of hemophilia)				
IT	Antibodies RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (anti-idiotypic; epitopes of factor VIII for treatment and diagnosis of hemophilia)				
IT	Affinity B cell (lymphocyte) Blood serum Coagulation Epitopes Filters Hemophilia Human Immunotherapy Liquid chromatographic columns T cell (lymphocyte)				

Test kits
(epitopes of **factor VIII** for treatment and
diagnosis of **hemophilia**)

IT **Antibodies**
RL: ADV (Adverse effect, including toxicity); DGN (Diagnostic use); REM
(Removal or disposal); BIOL (Biological study); PROC (Process); USES
(Uses)
(epitopes of **factor VIII** for treatment and
diagnosis of **hemophilia**)

IT BCR (B cell receptors)
Phospholipids, biological studies
TCR (T cell receptors)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(epitopes of **factor VIII** for treatment and
diagnosis of **hemophilia**)

IT **Peptides, biological studies**
RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(epitopes of **factor VIII** for treatment and
diagnosis of **hemophilia**)

IT Circulation
(extracorporeal; epitopes of **factor VIII** for
treatment and diagnosis of **hemophilia**)

IT **Immunoglobulins**
RL: ADV (Adverse effect, including toxicity); DGN (Diagnostic use); REM
(Removal or disposal); BIOL (Biological study); PROC (Process); USES
(Uses)
(**fragments**; epitopes of **factor VIII** for
treatment and diagnosis of **hemophilia**)

IT Diagnosis
(serodiagnosis; epitopes of **factor VIII** for
treatment and diagnosis of **hemophilia**)

IT 9001-29-0, Factor X 9013-55-2, Blood-coagulation factor XI
109319-16-6
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(epitopes of **factor VIII** for treatment and
diagnosis of **hemophilia**)

IT **9001-27-8, Factor VIII** 177359-62-5
177359-63-6 177359-64-7 177359-65-8 177359-66-9 177359-67-0
177359-69-2 177359-70-5 177359-71-6 177359-73-8 177359-74-9
177359-75-0 177359-76-1 177359-77-2 433929-54-5 433929-55-6
433929-56-7 433929-57-8 433929-58-9 433929-59-0 433929-60-3
433929-61-4 433929-62-5 433929-63-6 433929-64-7 433929-65-8
433929-66-9 433929-67-0 433929-68-1 433929-69-2 433929-70-5
433929-71-6 433929-72-7
RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(epitopes of **factor VIII** for treatment and
diagnosis of **hemophilia**)

L101 ANSWER 2 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:73453 HCAPLUS
DN 134:130398
ED Entered STN: 01 Feb 2001
TI Modified **factor VIII**
IN Lollar, John S.
PA Emory University, USA
SO U.S., 86 pp., Cont.-in-part of U.S. 5,859,204.
CODEN: USXXAM
DT Patent
LA English
IC ICM C12P021-04
ICS C12P021-06; A61K035-14; C07K014-00

NCL 435069600

CC 16-6 (Fermentation and Bioindustrial Chemistry)

Section cross-reference(s): 3

FAN.CNT 12

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6180371	B1	20010130	US 1998-37601	19980310 <--
	CA 2258502	AA	19971231	CA 1997-2258502	19970626 <--
	CA 2258502	C	20030429		
	CA 2322508	AA	19990916	CA 1999-2322508	19990310 <--
	WO 9946274	A1	19990916	WO 1999-US5193	19990310 <--
	W: AU, CA, CN, CZ, HU, IL, JP, KR, MX, NO, NZ, PL, RU				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9929956	A1	19990927	AU 1999-29956	19990310 <--
	AU 747644	B2	20020516		
	EP 1062224	A1	20001227	EP 1999-911272	19990310 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002506076	T2	20020226	JP 2000-535651	19990310 <--
	NZ 506771	A	20021126	NZ 1999-506771	19990310 <--
	US 6458563	B1	20021001	US 2000-523656	20000310 <--
	NO 2000004497	A	20001107	NO 2000-4497	20000908 <--
	US 2003166536	A1	20030904	US 2002-131510	20020423 <--
	US 2003068785	A1	20030410	US 2002-187319	20020628 <--
PRAI	US 1996-670707	A2	19960626	<--	
	US 1992-864004	A2	19920407	<--	
	US 1994-212133	A2	19940311	<--	
	WO 1994-US13200	A2	19941115	<--	
	WO 1997-US11155	A2	19970626	<--	
	US 1998-37601	A	19980310	<--	
	WO 1999-US5193	W	19990310		
	US 1999-315179	A3	19990520		
	US 2000-523656	A3	20000310		
AB	Specific amino acid loci of human factor VIII interact with inhibitory antibodies of hemophilia patients who have developed such antibodies after being treated with factor VIII. Modified factor VIII is disclosed in which the amino acid sequence is changed by a substitution at one or more of the specific loci. The modified factor VIII is not inhibited by inhibitory antibodies against the A2 or C2 domain epitopes. The modified factor VIII is useful for hemophiliacs, either to avoid or prevent the action of inhibitory antibodies.				
ST	factor VIII human porcine hybrid immunogenicity decrease				
IT	Animal tissue culture (mammalian; modified factor VIII with decreased immunogenicity)				
IT	Immunity (modified factor VIII with decreased immunogenicity)				
IT	244065-54-1 244065-55-2 309307-00-4, Blood-coagulation factor VIII (human) RL: PRP (Properties) (amino acid sequence; modified factor VIII with decreased immunogenicity)				
IT	113189-02-9P, Factor VIII RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (modified factor VIII with decreased				

immunogenicity)
 IT 201874-76-2 243905-33-1
 RL: PRP (Properties)
 (nucleotide sequence; modified **factor VIII** with decreased immunogenicity)
 IT 140742-96-7 148391-60-0 153065-62-4 217895-20-0, 6: PN: WO0174903
 SEQID: 6 unclaimed DNA 217895-23-3, 8: PN: WO0168109 SEQID: 8 unclaimed
 DNA 243905-15-9, 7: PN: WO0168109 SEQID: 7 unclaimed DNA 243905-16-0,
 9: PN: WO0168109 SEQID: 9 unclaimed DNA 243905-17-1 243905-18-2
 243905-19-3 243905-20-6 243905-21-7 243905-22-8 243905-23-9
 243905-24-0 243905-25-1 243905-26-2 243905-27-3 243905-28-4
 243905-29-5 243905-30-8 243905-31-9 243905-32-0 250353-64-1
 309308-34-7, 1: PN: WO0071141 SEQID: 7 unclaimed DNA 309308-35-8, 2: PN:
 WO0071141 SEQID: 8 unclaimed DNA 309308-36-9, 3: PN: WO0071141 SEQID: 9
 unclaimed DNA 309308-37-0, 4: PN: WO0071141 SEQID: 10 unclaimed DNA
 309308-38-1, 5: PN: WO0071141 SEQID: 11 unclaimed DNA 309308-39-2, 6:
 PN: WO0071141 SEQID: 12 unclaimed DNA
 RL: PRP (Properties)
 (unclaimed nucleotide sequence; modified **factor VIII**)
 IT 150791-63-2, **Blood-coagulation factor**
VIII (mouse precursor reduced) 308390-66-1
 RL: PRP (Properties)
 (unclaimed **protein** sequence; modified **factor**
VIII)
 IT 309262-12-2
 RL: PRP (Properties)
 (unclaimed sequence; modified **factor VIII**)
 RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
 RE
 (1) Anon; EP 0306968 A2 1988 HCAPLUS
 (2) Anon; WO 9107438 1990 HCAPLUS
 (3) Anon; WO 9411503 1994 HCAPLUS
 (4) Anon; WO 9703191 1997 HCAPLUS
 (5) Anon; WO 9703193 1997 HCAPLUS
 (6) Church; Proc Natl Acad Sci USA 1984, V81, P6934 HCAPLUS
 (7) Dominguez, O; Nucleic Acids Res 1994, V22, P3247 HCAPLUS
 (8) Eaton, D; Biochemistry 1986, V25(26), P8343 HCAPLUS
 (9) Fulcher, C; Proc Natl Acad Sci USA 1985, V82, P7728 HCAPLUS
 (10) Gitchee, J; Nature 1984, V312, P326
 (11) Healy, J; Blood 1996, V88, P4209
 (12) Lollar; US 5364771 1994 HCAPLUS
 (13) Lollar; US 5663060 1997 HCAPLUS
 (14) Lubin; J Biol Chem 1994, V269, P8639 HCAPLUS
 (15) Nakai, H; Blood 1994, V84, P224a
 (16) Ochman, H; Biotech (N Y) 1990, V8, P759 MEDLINE
 (17) Parker, J; Biotechniques 1991, V10, P94 HCAPLUS
 (18) Parker, J; Nucleic Acids Res 1991, V19, P3055 HCAPLUS
 (19) Pittman; US 5563045 1996 HCAPLUS
 (20) Sarkar, G; PCK Meth Appl 1993, V2, P318 HCAPLUS
 (21) Scandella, D; Blood 1989, V74, P1618 HCAPLUS
 (22) Scandella, D; Blood 1993, V82(6), P1767 HCAPLUS
 (23) Scandella, D; Blood 1995, V86, P1811 HCAPLUS
 (24) Scandella, D; Proc Natl Acad Sci USA 1988, V85, P6152 HCAPLUS
 (25) Siebert, P; Nucleic Acids Res 1995, V23, P1087 HCAPLUS
 (26) Toole; US 4757006 1988 HCAPLUS
 (27) Toole; US 4868112 1989 HCAPLUS
 (28) Toole; Nature 1984, V312, P342 HCAPLUS
 (29) Toole; Proc Natl Acad Sci USA 1986, V83, P5939 HCAPLUS

L101 ANSWER 3 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
 AN 2000:841997 HCAPLUS
 DN 134:14739

ED Entered STN: 01 Dec 2000
 TI **Blood-coagulation factor VIII**
 variants and hybrids with decreased immunoreactivity and having
 procoagulant activity
 IN Lollar, John S.
 PA Emory University, USA
 SO PCT Int. Appl., 172 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM A61K035-14
 ICS C07H021-04; C12P021-04; C12P021-06
 CC 7-5 (Enzymes)
 Section cross-reference(s): 3, 15, 63

FAN.CNT 12

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000071141	A1	20001130	WO 2000-US13541	20000516
	W: AU, CA, JP				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 6376463	B1	20020423	US 1999-315179	19990520 <--
	EP 1200105	A1	20020502	EP 2000-932530	20000516
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
	JP 2003508019	T2	20030304	JP 2000-619444	20000516
	AU 765442	B2	20030918	AU 2000-50237	20000516
PRAI	US 1999-315179	A	19990520		
	US 1992-864004	A2	19920407	<--	
	US 1994-212133	A2	19940311	<--	
	WO 1994-US13200	A2	19941115	<--	
	US 1996-670707	A2	19960626	<--	
	WO 2000-US13541	W	20000516		
AB	Specific amino acid loci of human blood-coagulation factor VIII interact with inhibitory antibodies of hemophilia patients who have developed such antibodies after being treated with factor VIII. Modified factor VIII is disclosed in which the amino acid sequence is changed by a substitution at one or more amino acids of positions 484-508 of the A2 domain. The A2 domain epitope was identified by construction of human-porcine and human-mouse hybrid factor VIII mols. and by site-specific alanine-scanning mutagenesis of the A2 domain. The modified factor VIII variants are useful as clotting factor supplements for hemophiliacs.				
ST	coagulation factor VIII hybrid variant immunoreactivity procoagulant; sequence coagulation factor VIII hybrid variant; epitope mapping coagulation factor VIII A2 domain				
IT	Antibodies RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) (autoantibodies, immunoreactivity toward; blood-coagulation factor VIII variants and hybrids with decreased immunoreactivity and having procoagulant activity)				
IT	Coagulants Mouse Mutagenesis Protein engineering Swine (blood-coagulation factor VIII)				

- variants and hybrids with decreased immunoreactivity and having procoagulant activity)
- IT cDNA sequences
(for **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)
- IT Epitopes
(mapping; **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)
- IT **Protein sequences**
(of **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)
- IT **Hemophilia**
(treatment of; **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)
- IT 150791-63-2, **Blood-coagulation factor VIII** (mouse precursor reduced) 153065-59-9, 20-2351-
Blood-coagulation factor VIII (human precursor reduced) 244065-54-1, **Blood-coagulation factor VIII**, procoagulant (swine precursor) 244065-55-2, **Blood-coagulation factor VIII**, procoagulant [de-(B domain)] (swine precursor) 308390-66-1
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(amino acid sequence; **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)
- IT 113189-02-9D, **Blood-coagulation factor VIII**, site-specific and hybrid variants
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(**blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)
- IT 140742-96-7, DNA (human **blood-coagulation factor VIII** cDNA plus flanks) 148391-60-0, DNA (mouse **blood-coagulation factor VIII** cDNA plus flanks) 153065-62-4, DNA (swine **blood-coagulation factor VIII** fragment-specifying cDNA) 201874-76-2, DNA (swine **blood-coagulation factor VIII** cDNA plus flanks) 243905-33-1, DNA (swine procoagulant **blood-coagulation factor VIII** [de-(B domain)] precursor-specifying cDNA plus flanks)
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(nucleotide sequence; **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)
- IT 217895-20-0, 6: PN: WO0174903 SEQID: 6 unclaimed DNA 217895-23-3, 8: PN: WO0168109 SEQID: 8 unclaimed DNA 243905-15-9, 7: PN: WO0168109 SEQID: 7 unclaimed DNA 243905-16-0, 9: PN: WO0168109 SEQID: 9 unclaimed DNA
243905-17-1 243905-18-2 243905-19-3 243905-20-6 243905-21-7
243905-22-8 243905-23-9 243905-24-0 243905-25-1 243905-27-3
243905-28-4 243905-29-5 243905-30-8 243905-31-9 243905-32-0
250353-64-1 309308-34-7, 1: PN: WO0071141 SEQID: 7 unclaimed DNA
309308-35-8, 2: PN: WO0071141 SEQID: 8 unclaimed DNA 309308-36-9, 3: PN:

WO0071141 SEQID: 9 unclaimed DNA 309308-37-0, 4: PN: WO0071141 SEQID: 10
 unclaimed DNA 309308-38-1, 5: PN: WO0071141 SEQID: 11 unclaimed DNA
 309308-39-2, 6: PN: WO0071141 SEQID: 12 unclaimed DNA
 RL: PRP (Properties)

(unclaimed nucleotide sequence; **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)

IT 243905-26-2 309262-12-2

RL: PRP (Properties)

(unclaimed sequence; **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Amano; Blood 1998, V91(2), P538 HCAPLUS
- (2) Fulcher; Proc Natl Acad Sci 1985, V82, P7728 HCAPLUS
- (3) Lollar; J Biol Chem 1992, V267(33), P23652 HCAPLUS
- (4) Scandella; Proc Natl Acad Sci 1988, V85, P6152 HCAPLUS

L101 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 1999:736932 HCAPLUS

DN 131:350266

ED Entered STN: 19 Nov 1999

TI Method for diagnosis and treatment of **haemophilia-A** patients with **factor VIII** inhibitors

IN Voorberg, Johannes Jacobus; Van Den Brink, Edward Norbert; Turenhout, Ellen Anne Maria

PA Stichting Sanquin Bloedvoorziening, Neth.

SO PCT Int. Appl., 61 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C12N015-13

ICS C07K016-36; C07K016-42; A61K039-395; A61K038-37; C12Q001-68; A61K039-395; A61K038-37

CC 15-3 (Immunochemistry)

Section cross-reference(s): 1, 3, 14

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9958680	A2	19991118	WO 1999-NL285	19990507 <--
	WO 9958680	A3	20010222		
	W: AU, CA, JP, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2327587	AA	19991118	CA 1999-2327587	19990507 <--
	AU 9938538	A1	19991129	AU 1999-38538	19990507 <--
	AU 760678	B2	20030522		
	EP 1095143	A2	20010502	EP 1999-921292	19990507 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002514422	T2	20020521	JP 2000-548471	19990507 <--
PRAI	EP 1998-201543	A	19980508	<--	
	WO 1999-NL285	W	19990507		

AB Anti-**factor VIII** antibodies (**factor**

VIII inhibitors) present in the plasma of patients with acquired **hemophilia** were characterized by immunopptn. and neutralization

expts. The **antibodies** directed against the **factor**

VIII light chain consisted exclusively of **IgG4**. CDNAs coding for human **factor VIII** inhibitor are disclosed.

IgG4 specific probes and primers for detection of **factor VIII** inhibitors and for producing recombinant **polypeptides** are provided. An **antibody** directed against a human

factor VIII inhibitor is provided. Pharmaceutical compns. which contain recombinant **IgG4 Fv** fragment and **blood-coagulation factor VIII** also provided.

- ST human **factor VIII** inhibitor **IgG4** cDNA sequence; diagnosis therapy **hemophilia A** **factor VIII** inhibitor **IgG4**
- IT **Hemophilia**
(A; method for diagnosis and treatment of **hemophilia** -A patients with **factor VIII** inhibitors)
- IT **Protein motifs**
(CDR3 of **IgG4**; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT **Immunoglobulins**
RL: ADV (Adverse effect, including toxicity); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**G4**, **factor VIII** inhibitors, gene for, and recombinants, **Fv fragment** of; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT Test kits
(**IgG4** labeled primers and probes containing; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT Primers (nucleic acid)
Probes (nucleic acid)
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific, labeled; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT **Antibodies**
RL: ARU (Analytical role, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(against **IgG4** (**factor VIII** inhibitor); method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT cDNA sequences
(for **factor VIII** inhibitors (**IgG4**) of human; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT Oligonucleotides
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(labeled, with radioactive atom or group, enzyme, fluorescent or luminescent group, dye or biotin; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT Blood analysis
Gene therapy
Genetic engineering
Molecular cloning
(method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT Diagnosis
(mol.; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT **Protein sequences**
(of **factor VIII** inhibitors (**IgG4**) of human; method for diagnosis and treatment of **hemophilia-A**

- A patients with **factor VIII** inhibitors)
- IT Epitopes
(of **factor VIII** inhibitors, specificity of; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT Hemostatics
(pharmaceutical composition containing recombinant **IgG4 Fv** fragment and **factor VIII**; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT PCR (polymerase chain reaction)
(quant.; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT 9001-27-8, **Factor VIII**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**IgG4** as inhibitors of, pharmaceutical composition containing recombinant **IgG4 Fv** fragment and; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT 250281-75-5
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, conIgG1-4; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT 250281-76-6
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huIgG4; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT 226984-00-5
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huJH3forSal; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT 226984-08-3
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huJH4-5forSal; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT 226984-12-9
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huJH6forSal; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT 226983-94-4
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huJH1-2forSal; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT 250353-40-3
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huVH1backNco; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)
- IT 165888-40-4

- RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use);
ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG4 specific primer, huVH2aback; method for diagnosis and
treatment of **hemophilia-A** patients with
factor VIII inhibitors)
- IT 250353-46-9
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use);
ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG4 specific primer, huVH2backNco; method for diagnosis and
treatment of **hemophilia-A** patients with
factor VIII inhibitors)
- IT 165888-41-5
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use);
ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG4 specific primer, huVH3aback; method for diagnosis and
treatment of **hemophilia-A** patients with
factor VIII inhibitors)
- IT 250353-48-1
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use);
ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG4 specific primer, huVH3backNco; method for diagnosis and
treatment of **hemophilia-A** patients with
factor VIII inhibitors)
- IT 250281-77-7
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use);
ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG4 specific primer, huVH4aback; method for diagnosis and
treatment of **hemophilia-A** patients with
factor VIII inhibitors)
- IT 250281-86-8
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use);
ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG4 specific primer, huVH4backNco; method for diagnosis and
treatment of **hemophilia-A** patients with
factor VIII inhibitors)
- IT 250281-78-8
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use);
ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG4 specific primer, huVH5aback; method for diagnosis and
treatment of **hemophilia-A** patients with
factor VIII inhibitors)
- IT 250281-87-9
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use);
ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG4 specific primer, huVH5backNco; method for diagnosis and
treatment of **hemophilia-A** patients with
factor VIII inhibitors)
- IT 167731-78-4, PN: US5962255 SEQID: 61 unclaimed DNA
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use);
ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG4 specific primer, huVH6aback; method for diagnosis and
treatment of **hemophilia-A** patients with
factor VIII inhibitors)
- IT 250281-88-0
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use);
ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG4 specific primer, huVH6backNco; method for diagnosis and
treatment of **hemophilia-A** patients with
factor VIII inhibitors)
- IT 165888-39-1
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use);
ANST (Analytical study); BIOL (Biological study); USES (Uses)
(IgG4 specific primer, huVH1aback; method for diagnosis and

treatment of **hemophilia-A** patients with
factor VIII inhibitors)

IT 250207-98-8P 250207-99-9P 250281-89-1P 250282-00-9P 250282-09-8P
250282-10-1P 250282-11-2P 250282-12-3P 250282-13-4P 250282-14-5P
250282-15-6P 250282-18-9P 250282-22-5P

RL: ADV (Adverse effect, including toxicity); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(**amino acid** sequence; method for diagnosis and
treatment of **hemophilia-A** patients with
factor VIII inhibitors)

IT 225914-21-6 225914-22-7 250285-51-9 250285-52-0 250285-53-1
250285-54-2

RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); USES (Uses)

(**nucleotide** sequence; method for diagnosis and treatment of
hemophilia-A patients with **factor**
VIII inhibitors)

L101 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 1999:595190 HCAPLUS

DN 131:227661

ED Entered STN: 21 Sep 1999

TI Modified **factor VIII**

IN Lollar, John S.

PA Emory University, USA

SO PCT Int. Appl., 187 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07H021-00

ICS C07K014-755; C12N015-11; C12N015-12

CC 15-2 (Immunochemistry)

Section cross-reference(s): 3, 14

FAN.CNT 12

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9946274	A1	19990916	WO 1999-US5193	19990310 <--
	W: AU, CA, CN, CZ, HU, IL, JP, KR, MX, NO, NZ, PL, RU				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 6180371	B1	20010130	US 1998-37601	19980310 <--
	CA 2322508	AA	19990916	CA 1999-2322508	19990310 <--
	AU 9929956	A1	19990927	AU 1999-29956	19990310 <--
	AU 747644	B2	20020516		
	EP 1062224	A1	20001227	EP 1999-911272	19990310 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002506076	T2	20020226	JP 2000-535651	19990310 <--
	NZ 506771	A	20021126	NZ 1999-506771	19990310 <--
	NO 2000004497	A	20001107	NO 2000-4497	20000908 <--
PRAI	US 1998-37601	A	19980310 <--		
	US 1996-670707	A2	19960626 <--		
	WO 1999-US5193	W	19990310		

AB Specific **amino acid** loci of human **factor**
VIII interact with inhibitory **antibodies** of
hemophilia patients who have developed such **antibodies**
after being treated with **factor VIII**. Modified
factor VIII is disclosed in which the **amino**
acid sequence is changed by a substitution at one or more of the
specific loci. The modified **factor VIII** may be hybrid

of human and porcine **factor VIII**. The modified **factor VIII** is not inhibited by inhibitory **antibodies** against the **A2** or **C2** domain epitopes. The modified **factor VIII** is useful for treating uncontrollable bleeding in **hemophiliacs**, either to avoid or prevent the action of inhibitory **antibodies**.

ST modified porcine human **factor VIII hemophilia**

IT **Hemophilia**

(**A**; modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT Blood-coagulation factors

RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(PCA (procoagulant activity); modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT **Antibodies**

RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)

(autoantibodies, inhibitory; modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT **Antibodies**

RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)

(inhibitory; modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT **Hemophilia**

Molecular cloning

Protein sequences

cDNA sequences

(modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT DNA

RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT Hemorrhage

(uncontrollable; modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT 153065-59-9 201874-16-0 201874-17-1 201874-18-2 201874-19-3
244060-57-9 244060-64-8 244065-54-1 244065-55-2 244065-56-3

RL: PRP (Properties)

(amino acid sequence; modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT 113189-02-9DP, **Factor VIII**, analogs

RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT 140742-96-7 201874-20-6 201874-21-7 201874-22-8 201874-23-9
 201874-76-2 243905-33-1 244065-57-4 244065-58-5 244065-59-6

RL: PRP (Properties)

(nucleotide sequence; modified and/or hybrid human and porcine
factor VIII for preventing uncontrollable bleeding in
hemophiliacs without provoking inhibitory **antibodies**)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Eaton, D; Biochemistry 1986, V25(26), P8343 HCAPLUS
- (2) Lollar; US 5663060 A 1997 HCAPLUS
- (3) Pittman; US 5563045 A 1996 HCAPLUS
- (4) Scandella, D; Blood 1995, V86(5), P1811 HCAPLUS

L101 ANSWER 6 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 1999:404859 HCAPLUS

DN 131:57772

ED Entered STN: 01 Jul 1999

TI Methods to treat undesirable immune responses

IN Conti-Fine, Bianca M.

PA Regents of the University of Minnesota, USA

SO PCT Int. Appl., 221 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K039-00

CC 15-2 (Immunochimistry)

Section cross-reference(s): 2, 3

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9930736	A2	19990624	WO 1998-US26787	19981216 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2315537	AA	19990624	CA 1998-2315537	19981216 <--
AU 9931799	A1	19990705	AU 1999-31799	19981216 <--
EP 1037663	A2	20000927	EP 1998-967008	19981216 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI US 1997-991143 A2 19971216 <--

WO 1998-US26787 W 19981216

AB Isolated and purified **peptides** and variants thereof, useful to prevent or treat **antibody**-mediated diseases, or indications caused by an undesirable **antibody** response to a given antigen, are provided. Also provided are **peptides** and methods useful to prevent or treat indications associated with the use of viral vectors in gene replacement therapy. Further, a method to inhibit or prevent aberrant immune responses to exogenous, non-infectious antigen is provided. The antigen associated with the **antibody**-mediated disease is an endogenous antigen such as acetylcholine receptor, insulin, growth hormone, **factor VIII** or factor IX; or an exogenous antigen such as fungal antigen, plant antigen, domestic cat antigen or mite allergen. The **antibody**-mediated disease is an autoimmune disease, allergic disease, systemic lupus erythematosus, pemphigus, thrombic thrombocytopenic purpura, **hemophilia A**, **hemophilia B**, or myasthenia gravis.

ST antigen T cell epitope **antibody** disease; autoimmune disease

allergy T cell epitope; acetylcholine receptor epitope myasthenia gravis;
factor VIII IX epitope hemophilia; gene
 therapy recombinant retrovirus adenovirus vector

IT **Hemophilia**

(A; T cell epitope of endogenous or exogenous antigen for
 treating undesired **antibody**-mediated diseases)

IT Cell activation

(B cell, inhibitor; T cell epitope of endogenous or exogenous
 antigen for treating undesired **antibody**-mediated diseases)

IT **Hemophilia**

(B; T cell epitope of endogenous or exogenous antigen for
 treating undesired **antibody**-mediated diseases)

IT **Immunoglobulins**

RL: ADV (Adverse effect, including toxicity); BSU (Biological study,
 unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM
 (Formation, nonpreparative)

(G1; T cell epitope of endogenous or exogenous antigen for treating
 undesired **antibody**-mediated diseases)

IT **Immunoglobulins**

RL: ADV (Adverse effect, including toxicity); BSU (Biological study,
 unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM
 (Formation, nonpreparative)

(G; T cell epitope of endogenous or exogenous antigen for
 treating undesired **antibody**-mediated diseases)

IT Animal

(SCID; T cell epitope of endogenous or exogenous antigen for treating
 undesired **antibody**-mediated diseases)

IT Allergy

Animal virus
 Autoimmune disease
 Bacteria (Eubacteria)
 CD4-positive T cell
 Cystic fibrosis
 Drugs
 Epitopes
 Gene therapy
Hemophilia
 Hemorrhage
 Immune tolerance
 Immunosuppressants
 Infection
 Mammal (Mammalia)
 Myasthenia gravis
 Plasmapheresis
 Respiratory tract
 T cell (lymphocyte)
 Virus vectors

(T cell epitope of endogenous or exogenous antigen for treating
 undesired **antibody**-mediated diseases)

IT **Antibodies**

Antigens

RL: ADV (Adverse effect, including toxicity); BSU (Biological study,
 unclassified); BIOL (Biological study)

(T cell epitope of endogenous or exogenous antigen for treating
 undesired **antibody**-mediated diseases)

IT Allergens

Cholinergic receptors

RL: ADV (Adverse effect, including toxicity); BSU (Biological study,
 unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(T cell epitope of endogenous or exogenous antigen for treating
 undesired **antibody**-mediated diseases)

IT Muscle, disease

(animal model; T cell epitope of endogenous or exogenous antigen for

treating undesired **antibody**-mediated diseases)

IT Disease, animal
(**antibody**-mediated; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Cat (Felis catus)
Fungi
Mite and Tick
Plant (Embryophyta)
(antigen; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT **Antibodies**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(autoantibodies; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Antigens
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(autoantigens; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Disease, animal
(deficiency; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT T cell (lymphocyte)
(helper cell/inducer, TH2, down-regulation; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Hematopoietic precursor cell
(human; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Drug delivery systems
(injections, s.c.; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Diabetes mellitus
(insulin-dependent; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Drug delivery systems
(nasal; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Disease models
(non-human mammalian; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Skin, disease
(pemphigus; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Virus
(recombinant; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Immunodeficiency
(severe combined, animal; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Lupus erythematosus
(systemic; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Purpura (disease)
(thrombocytopenic, thrombic; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Adenoviridae
Retroviridae
(vector; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT **Proteins, general, biological studies**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
 (virus-specific; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT 9001-28-9, Factor IX 9002-72-6, Growth hormone 9004-10-8, Insulin, biological studies 109319-16-6, **Factor VIII**
 RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
 (T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT 9026-93-1, Adenosine deaminase
 RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

L101 ANSWER 7 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
 AN 1998:219210 HCAPLUS
 DN 128:317097
 ED Entered STN: 18 Apr 1998
 TI A human alloantibody interferes with binding of factor IXa to the **factor VIII** light chain
 AU Fijnvandraat, Karin; Celie, Patrick H. N.; Turenhout, Ellen A. M.; ten Cate, Jan W.; Van Mourik, Jan A.; Mertens, Koen; Peters, Marjolein; Voorberg, Jan
 CS Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Departments of Blood Coagulation and Plasma Protein Technology, Amsterdam, 1066 CX, Neth.
 SO Blood (1998), 91(7), 2347-2352
 CODEN: BLOOAW; ISSN: 0006-4971
 PB W. B. Saunders Co.
 DT Journal
 LA English
 CC 1-8 (Pharmacology)
 AB Inhibitory **antibodies** directed against **factor VIII** develop in a substantial number of patients with **hemophilia A** as a consequence of **factor VIII** replacement therapy. These **antibodies** usually recognize discrete epitopes within the **A2** and/or the **C2** domains of **factor VIII**. Here, the authors have characterized the **antibodies** present in the plasma of a patient affected by severe **hemophilia A**. The **antibodies** reacted readily with the metabolically labeled **factor VIII** light chain and fragments thereof when analyzed by immunopptn. The inhibitory activity could be neutralized by the complete light chain, whereas only slight neutralization occurred with a fragment comprising the isolated **C2** domain. Binding of the majority of **antibodies** to in vitro synthesized **factor VIII** fragments was dependent on the presence of **amino acid** residues Gln1778-Met1823, a region known to contain a **factor IXa** binding site. Functional characterization showed that purified **IgG** from the patient's serum inhibited binding of **factor IXa** to immobilized **factor VIII** light chain in a dose-dependent manner. These data indicate that human alloantibodies may inhibit **factor VIII** activity by interfering with **factor IXa**-**factor VIIIa** complex assembly.

ST alloantibody coagulation factor IXa VIII
 IT **Hemophilia**
 (A; human alloantibody interferes with binding of coagulation factor IXa to **factor VIII** light chain)

IT **Immunoglobulins**
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (G; human alloantibody interferes with binding of coagulation factor IXa to **factor VIII** light

chain)
IT **Antibodies**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(alloantibodies; human alloantibody interferes with binding of
coagulation factor IXa to **factor VIII** light chain)
IT Drug resistance
(human alloantibody interferes with binding of coagulation factor IXa
to **factor VIII** light chain)
IT 37316-87-3, Blood coagulation factor IXa
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(human alloantibody interferes with binding of coagulation factor IXa
to **factor VIII** light chain)
IT 109319-16-6, Blood-coagulation factor
VIII
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP
(Properties); BIOL (Biological study); PROC (Process)
(human alloantibody interferes with binding of coagulation factor IXa
to **factor VIII** light chain)

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

- (1) Arai, M; J Clin Invest 1989, V83, P1978 HCAPLUS
- (2) Bray, G; Blood 1994, V83, P2428 MEDLINE
- (3) de Biasi, R; Thromb Haemost 1994, V71, P544 MEDLINE
- (4) Fijnvandraat, K; Blood 1997, V89, P4371 HCAPLUS
- (5) Fulcher, C; Proc Natl Acad Sci USA 1985, V82, P7728 HCAPLUS
- (6) Healey, J; J Biol Chem 1995, V270, P14505 HCAPLUS
- (7) Hoyer, L; N Engl J Med 1994, V330, P38 MEDLINE
- (8) Kasper, C; Thromb Diath Haemorrh 1975, V34, P869
- (9) Lenting, P; J Biol Chem 1994, V269, P7150 HCAPLUS
- (10) Lenting, P; J Biol Chem 1996, V271, P1935 HCAPLUS
- (11) Leyte, A; Biochem J 1989, V263, P187 HCAPLUS
- (12) Leyte, A; Biochem J 1989, V257, P679 HCAPLUS
- (13) Lollar, P; J Biol Chem 1988, V263, P10451 HCAPLUS
- (14) Lollar, P; J Clin Invest 1994, V93, P2497 HCAPLUS
- (15) Lusher, J; N Engl J Med 1993, V328, P453 MEDLINE
- (16) Mertens, K; Br J Haematol 1993, V85, P133 HCAPLUS
- (17) Saenko, E; J Biol Chem 1994, V269, P11601 HCAPLUS
- (18) Saenko, E; J Biol Chem 1996, V271, P27424 HCAPLUS
- (19) Scandella, D; Blood 1989, V74, P1618 HCAPLUS
- (20) Scandella, D; Blood 1993, V82, P1767 HCAPLUS
- (21) Scandella, D; Blood 1995, V86, P1811 HCAPLUS
- (22) Scandella, D; Proc Natl Acad Sci USA 1988, V85, P6152 HCAPLUS
- (23) Scandella, D; Thromb Haemost 1992, V67, P665 HCAPLUS
- (24) Shima, M; Thromb Haemost 1993, V69, P240 HCAPLUS
- (25) Suzuki, T; Thromb Haemost 1996, V76, P749 HCAPLUS
- (26) Toole, J; Nature 1984, V312, P342 HCAPLUS
- (27) Vehar, G; Nature 1984, V312, P337 HCAPLUS
- (28) Veltkamp, J; Thromb Diath Haemorrh 1968, V19, P279 MEDLINE
- (29) Zhong, D; Blood 1996, V88, P324a

L101 ANSWER 8 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 1997:718000 HCAPLUS

DN 127:356538

ED Entered STN: 13 Nov 1997

TI construction of inactivation resistant **factor VIII**
procoagulant and applications to **hemophilia** treatment

IN Kaufman, Randal J.; Pipe, Steven W.; Amano, Kagehiro

PA Regents of the University of Michigan, USA; Kaufman, Randal J.; Pipe,
Steven W.; Amano, Kagehiro

SO PCT Int. Appl., 57 pp.

CODEN: PIXXD2

DT Patent

LA English
 IC ICM C12N009-48
 ICS C12N015-63; C12N001-21; C07H021-04; A61K038-48; A61K039-395
 CC 7-5 (Enzymes)
 Section cross-reference(s): 14

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9740145	A1	19971030	WO 1997-US6563	19970424 <--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9732027	A1	19971112	AU 1997-32027	19970424 <--
	EP 910628	A1	19990428	EP 1997-927596	19970424 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2000511407	T2	20000905	JP 1997-538216	19970424 <--
	US 2003148953	A1	20030807	US 2002-283648	20021029 <--
PRAI	US 1996-16117P	P	19960424 <--		
	US 1996-17785P	P	19960515 <--		
	WO 1997-US6563	W	19970424 <--		
	US 1997-980038	B1	19971126 <--		
	US 2001-819098	A2	20010411		
	US 2002-122264	A2	20020411		

AB Novel purified and isolated nucleic acid sequences encoding procoagulant-active **FVIII proteins** are described. To determine whether specific **amino acid** sequences within **FVIII A-domain** inhibit secretion, chimeric **proteins** containing the **A1** and **A2-domains** of **FVIII** or **FV** were studied. The nucleic acid sequences of encode **amino acid** sequences corresponding to known human **FVIII** sequences where residue Phe309 is mutated. The nucleic acid sequences also encode human **FVIII** sequences where the APC cleavage sites, Arg336 and Ile562, are mutated. The nucleic acid sequences of sequences corresponding to known human **FVIII** sequences where the **B-domain** is deleted, the **von Willebrand factor** binding site is deleted, a thrombin cleavage site is mutated and an **amino acid** sequence spacer is inserted between the **A2-** and **A3-domains**. These nucleotide encode **factor VIII proteins** capable of secretion at levels higher than typically obtained with wild-type **factor VIII**. Methods of producing the **FVIII proteins** and pharmaceutical compns. containing the nucleotide sequences or **proteins** as well as methods of treating patients suffering from **hemophilia** are also provided. A lower dosage of **protein** may be administered to the **hemophiliac** patient during **FVIII** replacement therapy. By utilizing the **proteins** described, the total exposure of **protein** to the patient is reduced, thereby lowering the likelihood of inhibitor formation.

ST inactivation resistant **factor VIII** procoagulant **hemophilia**

IT **Antibodies**

RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
 (anti-light chain **antibody** ESH8 [inducing **FVIII** binding to vWF used to stabilize inactivation resistant **FVIII**])

-]; 2248-2285 procoagulant epitope recognition; construction of inactivation resistant **factor VIII** procoagulant)
- IT **Hemophilia**
(applications for treatment of; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)
- IT Drug delivery systems
Gene therapy
Secretion (process)
(construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)
- IT Epitopes
(epitope of 2248 to 2285 of **Blood-coagulation factor VIII** procoagulant; **antibody** recognizing; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)
- IT Crosslinking
(inducing **FVIII** binding to vWF used to stabilize inactivation resistant **FVIII**; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)
- IT **Proteins, specific or class**
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(modified; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)
- IT **109319-16-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(anti-light chain **antibody** ESH8 and crosslinkers inducing **FVIII** binding to vWF; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)
- IT 42617-41-4, Activated **protein c**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(generation of **protein** resistant to cleavage by; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)
- IT **113189-02-9DP**, derivs
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(modified **peptides** of; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)
- IT 9002-04-4, Thrombin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(structural and functional stability of IR8 during thrombin cleavage; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)

L101 ANSWER 9 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 1997:710503 HCAPLUS

DN 128:31607

ED Entered STN: 10 Nov 1997

TI Characterization of a genetically engineered inactivation-resistant **coagulation factor VIIIA**

AU Pipe, Steven W.; Kaufman, Randal J.

CS Department of Pediatrics, University of Michigan Medical Center, Ann Arbor, MI, 48109, USA

SO Proceedings of the National Academy of Sciences of the United States of America (1997), 94(22), 11851-11856
CODEN: PNASA6; ISSN: 0027-8424

PB National Academy of Sciences

DT Journal

LA English

CC 6-3 (General Biochemistry)

AB Individuals with **hemophilia A** require frequent infusion of preps. of **coagulation factor VIII**. The activity of **factor VIII (FVIII)** as a cofactor for factor IXa in the coagulation cascade is limited by its instability after activation by thrombin. Activation of **FVIII** occurs through proteolytic cleavage and generates an unstable **FVIII** heterotrimer that is subject to rapid dissociation of its subunits. In addition, further proteolytic cleavage by thrombin, factor Xa, factor IXa, and activated **protein C** can lead to inactivation. We have engineered and characterized a **FVIII protein, IR8**, that has enhanced in vitro stability of **FVIII** activity due to resistance to subunit dissociation and proteolytic inactivation. **FVIII** was genetically engineered by deletion of residues 794-1689 so that the **A2** domain is covalently attached to the light chain. Missense mutations at thrombin and activated **protein C** inactivation cleavage sites provided resistance to proteolysis, resulting in a single-chain **protein** that has maximal activity after a single cleavage after arginine-372. The specific activity of partially purified **protein** produced in transfected COS-1 monkey cells was 5-fold higher than wild-type (WT) **FVIII**. Whereas WT **FVIII** was inactivated by thrombin after 10 min in vitro, IR8 still retained 38% of peak activity after 4 h. Whereas binding of IR8 to **von Willebrand factor (vWF)** was reduced 10-fold compared with WT **FVIII**, in the presence of an anti-light chain **antibody**, ESH8, binding of IR8 to vWF increased 5-fold. These results demonstrate that residues 1690-2332 of **FVII** are sufficient to support high-affinity vWF binding. Whereas ESH8 inhibited WT **factor VIII** activity, IR8 retained its activity in the presence of ESH8. We propose that resistance to **A2** subunit dissociation abrogates inhibition by the ESH8 **antibody**. The stable **FVIIIa** described here provides the opportunity to study the activated form of this critical coagulation factor and demonstrates that **proteins** can be improved by rationale design through genetic engineering technol.

ST factor VIIIa von Willebrand binding

IT **Blood-coagulation factors**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(**VIIIa**; characterization of a genetically engineered inactivation-resistant **coagulation factor VIIIa**)

IT **109319-16-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(characterization of a genetically engineered inactivation-resistant **coagulation factor VIIIa**)

RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Bihoreau, N; Biochem J 1991, V277, P23 HCAPLUS
- (2) Eaton, D; Biochemistry 1986, V25, P505 HCAPLUS
- (3) Eaton, D; Biochemistry 1986, V25, P8343 HCAPLUS
- (4) Erlich, H; PCR Technology: Principles and Applications for DNA Amplification 1989
- (5) Fay, P; Biochim Biophys Acta 1986, V871, P268 HCAPLUS
- (6) Fay, P; Biochim Biophys Acta 1988, V952, P181 HCAPLUS
- (7) Fay, P; J Biol Chem 1991, V266, P20139 HCAPLUS

- (8) Fay, P; J Biol Chem 1991, V266, P2172 HCAPLUS
- (9) Fay, P; J Biol Chem 1991, V266, P8957 HCAPLUS
- (10) Fay, P; J Biol Chem 1993, V268, P17861 HCAPLUS
- (11) Fay, P; J Biol Chem 1994, V269, P20522 HCAPLUS
- (12) Fay, P; J Biol Chem 1996, V271, P6027 HCAPLUS
- (13) Foster, P; Blood 1990, V75, P1999 HCAPLUS
- (14) Fulcher, C; Blood 1984, V63, P486 HCAPLUS
- (15) Girma, J; Blood 1987, V70, P605 HCAPLUS
- (16) Gitschier, J; Blood 1988, V72, P1022 HCAPLUS
- (17) Hamer, R; Eur J Biochem 1987, V167, P253 HCAPLUS
- (18) Johnson, D; Thromb Haemostasis 1994, V71, P428 HCAPLUS
- (19) Kaufman, R; J Biol Chem 1988, V263, P6352 HCAPLUS
- (20) Kaufman, R; Methods Enzymol 1990, V185, P487 HCAPLUS
- (21) Koedam, J; Eur J Biochem 1990, V189, P229 HCAPLUS
- (22) Lenting, P; J Biol Chem 1996, V271, P1935 HCAPLUS
- (23) Lenting, P; J Biol Chem 1996, V271, P25332 HCAPLUS
- (24) Leyte, A; Biochem J 1989, V257, P679 HCAPLUS
- (25) Lollar, P; J Biol Chem 1990, V265, P1688 HCAPLUS
- (26) Lynch, C; Hum Gene Ther 1993, V4, P259 HCAPLUS
- (27) Mertens, K; Thromb Haemostasis 1985, V54, P654 HCAPLUS
- (28) Meulien, P; Protein Eng 1988, V2, P301 HCAPLUS
- (29) Michnick, D; J Biol Chem 1994, V269, P20095 HCAPLUS
- (30) Nesheim, M; J Biol Chem 1991, V266, P17815 HCAPLUS
- (31) O'Brien, L; J Biol Chem 1995, V270, P27087 HCAPLUS
- (32) Pipe, S; J Biol Chem 1996, V271, P25671 HCAPLUS
- (33) Pittman, D; Blood 1993, V81, P2925 HCAPLUS
- (34) Pittman, D; Blood 1994, V84, P4214 HCAPLUS
- (35) Pittman, D; Methods Enzymol 1993, V222, P236 HCAPLUS
- (36) Pittman, D; Proc Natl Acad Sci USA 1988, V85, P2429 HCAPLUS
- (37) Regan, L; J Biol Chem 1995, V270, P8546 HCAPLUS
- (38) Saenko, E; J Biol Chem 1994, V269, P11601 HCAPLUS
- (39) Saenko, E; J Biol Chem 1996, V271, P27424 HCAPLUS
- (40) Sarver, N; DNA 1987, V6, P553 HCAPLUS
- (41) Scandella, D; Blood 1995, V86, P1811 HCAPLUS
- (42) Shima, M; Int J Hematol 1991, V54, P515 HCAPLUS
- (43) Toole, J; Nature (London) 1984, V312, P342 HCAPLUS
- (44) Toole, J; Proc Natl Acad Sci USA 1986, V83, P5939 HCAPLUS
- (45) van Dieijen, G; J Biol Chem 1981, V256, P3433 HCAPLUS
- (46) Vehar, G; Nature (London) 1984, V312, P337 HCAPLUS
- (47) Weiss, H; J Clin Invest 1977, V60, P390 HCAPLUS
- (48) Zatloukal, K; Proc Natl Acad Sci USA 1994, V91, P5148 HCAPLUS

L101 ANSWER 10 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 1997:413693 HCAPLUS

DN 127:144671

ED Entered STN: 03 Jul 1997

TI Analysis of **factor VIII** inhibitors using hybrid
human/porcine **factor VIII**

AU Lollar, Pete

CS Department Medicine, Emory University, Atlanta, GA, 30322, USA

SO Thrombosis and Haemostasis (1997), 78(1), 647-651

CODEN: THHADQ; ISSN: 0340-6245

PB Schattauer

DT Journal; General Review

LA English

CC 1-0 (Pharmacology)

AB A review with 39 refs. is given on anal. of **factor VIII**

inhibitors using hybrid human/porcine **factor VIII**.

Recombinant hybrid human/porcine **factor VIII** mols.

were used to map a major determinant of the epitope recognized by human
anti-**factor VIII A2** domain inhibitory

antibodies to a region bounded by human **fVIII** residues

Arg484-Ile508. This approach is used to characterize the C2

domain inhibitor epitope. The process of creating hybrid human/porcine **factor VIII** mols. to map inhibitor epitopes produces procoagulant active **fVIII** with reduced reactivity with clin. **factor VIII** inhibitors. This suggests that it may be possible to develop of a hybrid human/porcine **factor VIII** that is useful in the management of **hemophilia A** and acquired **hemophilia**.

ST review **factor VIII** inhibitor amino acid

IT **Protein sequences**

(anal. of **factor VIII** inhibitors using hybrid human/porcine **factor VIII**)

IT 113189-02-9, **Factor VIII**

RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(anal. of **factor VIII** inhibitors using hybrid human/porcine **factor VIII**)

L101 ANSWER 11 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 1997:394590 HCAPLUS

DN 127:107880

ED Entered STN: 26 Jun 1997

TI The missense mutation Arg593 → Cys is related to **antibody** formation in a patient with mild **hemophilia A**

AU Fijnvandraat, Karin; Turenhout, Ellen A. M.; van den Brink, Edward N.; ten Cate, Jan W.; van Mourik, Jan A.; Peters, Marjolein; Voorberg, Jan

CS Dep. Blood Coagulation, Central Lab. Netherlands Red Cross Blood Transfusion Serv., Amsterdam, 1066 CX, Neth.

SO Blood (1997), 89(12), 4371-4377

CODEN: BLOOAW; ISSN: 0006-4971

PB Saunders

DT Journal

LA English

CC 15-8 (Immunochemistry)

Section cross-reference(s): 1

AB The development of inhibitory **antibodies** to **factor VIII** in patients affected by a mild form of **hemophilia A** (**factor VIII** > 0.05 IU/mL) is considered a

rare event. In this study, the authors evaluated the relation between genotype and anti-**factor VIII** **antibody** formation in a patient with mild **hemophilia A**.

Mutation anal. showed that a missense mutation in the **factor VIII** gene leading to replacement of Arg593 by Cys in the **A2** domain of **factor VIII** was associated with **hemophilia A** in this patient. The anti-**factor**

VIII **antibodies** present in the patient's plasma were characterized using metabolically labeled **factor VIII** fragments expressed in insect cells. The anti-**factor**

VIII **antibodies**, composed of subclasses IgG2 and IgG4, reacted with both the fragment corresponding to the **factor VIII** heavy chain and the **A2** domain.

The Arg593 → Cys substitution was introduced into the cDNA encoding the **A2** domain of **factor VIII** and the resulting construct was expressed in insect cells. Strikingly, the metabolically labeled **A2** domain carrying the Arg593 → Cys mutation was not recognized by the anti-**factor VIII**

antibodies present in the plasma of the patient. These data indicate that the antifactor **VIII** **antibodies** are exclusively directed against exogenous **factor VIII**. This strongly suggests that the Arg593 → Cys substitution results in recognition of wild-type **factor VIII** as nonself and is thereby related to the formation of anti-**factor VIII**

antibodies after **factor VIII** replacement therapy in this particular patient.

ST **hemophilia A** missense mutation **antibody FVIII**; **factor VIII** mutation **hemophilia A antibody**

IT **Protein motifs**

(A2 domain; missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT **Hemophilia**

(A; missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT Gene, animal

RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)

(F8; missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT **Immunoglobulins**

RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)

(G2, anti-**factor VIII**; missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT **Immunoglobulins**

RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)

(G4, anti-**factor VIII**; missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT **Antibodies**

RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)

(anti-**factor VIII**; missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT **Genotypes**

(missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT **Mutation**

(missense, R593C; missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT **113189-02-9, Coagulation factor VIIIc**

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological

process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)
 (missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

L101 ANSWER 12 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 1997:317203 HCAPLUS

DN 127:3893

ED Entered STN: 17 May 1997

TI Identification of novel **factor VIII** inhibitor epitopes using synthetic **peptide** arrays

AU Palmer, Douglas S.; Dudani, Anil K.; Drouin, Jeanne; Ganz, Peter R.
 CS Ottawa Centre, Canadian Red Cross Society, Blood Services, University of Ottawa, Can.

SO Vox Sanguinis (1997), 72(3), 148-161
 CODEN: VOSAAD; ISSN: 0042-9007

PB Karger

DT Journal

LA English

CC 15-2 (Immunochemistry)

AB Mapping the **antibody**-binding sites on the **factor VIII (FVIII) protein** opens the prospect of studying the development of **FVIII** inhibitors and the alteration of inhibitor specificities over time. This paper describes a novel approach to the mapping of **FVIII antibody**-binding sites. Immobilized synthetic **peptide** arrays covering 80% of the complete 2351 **amino acid** sequence of **factor VIII (FVIII)** were used to determine epitope specificity of 6 alloantibodies and 3 autoantibodies inhibitory to **FVIII** activity. This detailed assessment was carried out using a modified ELISA with plasma from normal persons or **hemophilia A** patients without inhibitors as neg. controls. **Antibody**-combining sites could be differentiated in both a qual. and quant. manner and were patient-specific. Highly reactive **peptides** were restricted to specific sites in the **A1-A3** and **C1-C2** domains and were not proximal to known proteolytic cleavage sites. Free **peptides** incubated in vitro with the plasmas of 3 patients significantly reduced residual inhibitor titers in a dose-dependent manner. This technique permits the study of the development and specificity of **FVIII** inhibitors, can detect and differentiate between inhibitory and noninhibitory **antibodies** using immobilized or free **peptides**, resp., permits correlation of **antibody**-combining sites with inhibition of **FVIII** activity and provides a basis for the development of inhibitor adsorption or neutralization technol.

ST **factor VIII** epitope mapping inhibitor **antibody**

IT **Antibodies**

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (alloantibodies; identification of novel **factor VIII** epitopes recognized by inhibitor **antibodies** using synthetic **peptide** arrays)

IT **Antibodies**

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (autoantibodies; identification of novel **factor VIII** epitopes recognized by inhibitor **antibodies** using synthetic **peptide** arrays)

IT **Epitopes**

(identification of novel **factor VIII** epitopes)

recognized by inhibitor **antibodies** using synthetic
peptide arrays)

IT **Peptides, biological studies**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(identification of novel **factor VIII** epitopes
recognized by inhibitor **antibodies** using synthetic
peptide arrays)

IT **Epitopes**
(mapping; identification of novel **factor VIII**
epitopes recognized by inhibitor **antibodies** using synthetic
peptide arrays)

IT **113189-02-9, Factor VIII**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(identification of novel **factor VIII** epitopes
recognized by inhibitor **antibodies** using synthetic
peptide arrays)

L101 ANSWER 13 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN

AN **1997:277036 HCAPLUS**

DN **127:49146**

ED Entered STN: 30 Apr 1997

TI Autoantibody selectively inhibits binding of **von**
Willebrand factor to **glycoprotein Ib**.
Recognition site is located in the **A1** loop of **von**
Willebrand factor

AU Mohri, Hiroshi; Yamazaki, Etsuko; Suzuki, Zekou; Takano, Toshikuni;
Yokota, Shumpei; Okubo, Takao

CS School Medicine, Yokohama City Univ., Yokohama, 236, Japan

SO Thrombosis and Haemostasis (1997), 77(4), 760-766
CODEN: THHADQ; ISSN: 0340-6245

PB Schattauer

DT Journal

LA English

CC 15-8 (Immunochemistry)
Section cross-reference(s): 7

AB In a severe von Willebrand disease an inhibitor was suggested directed
against vWF:RCO activity of **von Willebrand**
factor (vWF) without inhibition of the **FVIII:C**. The
inhibitor was identified as an **antibody** of **IgG** class.
The inhibitor inhibited the interaction of vWF in the presence of
ristocetin and that of asialo-vWF with GPIb while it partially blocked
botrocetin-mediated interaction of vWF to GPIb. The inhibitor reacted
with native vWF, the 39/34kDa fragment (**amino acids**
[aa] 480/481-718) and the recombinant vWF fragment (Male-rvWF508-704), but
not with Fragment III-T2 (heavy chains, aa 273-511; light chains, aa
674-728). A synthetic **peptide** (aa 514-542) did not inhibit
vWF-inhibitor complex formation. It was concluded that this is the 1st
autoantibody of class **IgG** from human origin that recognizes the
sequence in the **A1** loop of vWF, resulting in a virtual absence
of functional vWF and a concomitant severe bleeding tendency although
recognition site is different from the residues 514-542 which is crucial
for vWF-GPIb interaction.

ST autoantibody **IgG** von Willebrand disease

IT **Glycolipoproteins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(GPIb; **IgG** autoantibody to the **glycoprotein Ib**
binding domain of **von Willebrand factor**
in a human with von Willebrand disease)

IT **Enzyme functional sites**
Von Willebrand's disease
(**IgG** autoantibody to the **glycoprotein Ib** binding
domain of **von Willebrand factor** in a

human with von Willebrand disease)

IT **Immunoglobulins**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(autoantibodies, **G**; **IgG** autoantibody to the
glycoprotein Ib binding domain of **von**
Willebrand factor in a human with von Willebrand
disease)

IT Conformation
(**protein**; **IgG** autoantibody to the
glycoprotein Ib binding domain of **von**
Willebrand factor in a human with von Willebrand
disease)

IT **109319-16-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(**IgG** autoantibody to the **glycoprotein Ib** binding
domain of **von Willebrand factor** in a
human with von Willebrand disease)

L101 ANSWER 14 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1995:540270** HCAPLUS
DN **122:288519**
ED Entered STN: 10 May 1995
TI Selection and application of human single chain **Fv**
antibody fragments from a semi-synthetic phage **antibody**
display library with designed **CDR3** regions
AU Kruif, John De; Boel, Edwin; Logtenberg, Ton
CS Dep. of Immunology and Eykman-Winkler, Univ. of Utrecht, Utrecht, 3508 GA,
Neth.
SO Journal of Molecular Biology (1995), 248(1), 97-105
CODEN: JMOBAK; ISSN: 0022-2836
PB Academic
DT Journal
LA English
CC 15-3 (Immunochemistry)
Section cross-reference(s): 3
AB The authors have constructed a large (3.6+108 clones) phage display
library of human single chain **Fv** (**scFv**)
antibody fragments by combining 49 germline VH genes with
synthetic heavy chain **CDR3** (**HCDR3**) regions and seven light
chains. The **HCDR3** regions varied in length between 6 and 15 residues and
were designed to contain fully randomized stretches of **amino**
acid residues flanked by regions of limited residue variability
that were composed of **amino acid** residues that
frequently occur in natural **antibodies**. This approach should
increase the frequency of functional mols. in the library and, in addition,
make it possible to efficiently utilize available cloning space. By
direct selection on solid phase-bound antigens were obtained phage
antibodies with binding activities to 13 different antigens,
including **Von Willebrand factor**, the
DNA-binding HMG box of transcription factor TCF-1 and the tumor antigen
EGP-2. In addition, a competitive selection procedure was applied to target
phage **antibodies** to the desired portion of a recombinant fusion
protein and to select phage **antibodies** capable of
discriminating between the two highly homologous homeobox **proteins**
PBX1a and **PBX2**. The functional capacity of monoclonal phage
antibodies was assessed in immuno-histochem. staining of tissue
specimens, Western blotting assays and immunofluorescent anal. of cells by
flow cytometry. The results demonstrate that this large human phage
antibody library contains a broad assortment of binding
specificities that can be applied in a variety of biochem. assays.

ST **antibody Fv** fragment phage library
IT Antigens

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(EGP-2; **antibodies** from phage display library of human single chain **Fv antibody** fragments binding to)

IT Combinatorial library
Virus, bacterial
(phage display library of human single chain **Fv antibody** fragments)

IT **Antibodies**
RL: BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(phage display library of human single chain **Fv antibody** fragments)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(phage display library of human single chain **Fv antibody** fragments)

IT Ribonucleic acid formation factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TCF-1 (T-cell factor 1), **antibodies** from phage display library of human single chain **Fv antibody** fragments binding to)

IT **109319-16-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**antibodies** from phage display library of human single chain **Fv antibody** fragments binding to)

L101 ANSWER 15 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN

AN **1995:531444** HCAPLUS

DN **123:53000**

ED Entered STN: 06 May 1995

TI A 110-amino acid region within the A1-domain of **coagulation factor VIII** inhibits secretion from mammalian cells

AU Marquette, Kimberly A.; Pittman, Debra D.; Kaufman, Randal J.

CS Howard Hughes Med. Inst., Univ. Michigan Med. Cent., Ann Arbor, MI, 48105, USA

SO Journal of Biological Chemistry (1995), 270(17), 10297-303
CODEN: JBCHA3; ISSN: 0021-9258

PB American Society for Biochemistry and Molecular Biology

DT Journal

LA English

CC 13-5 (Mammalian Biochemistry)

AB **Factor VIII** is the coagulation factor deficient in the X-chromosome-linked bleeding disorder **hemophilia A**. **Factor VIII** is homologous to blood coagulation factor V, both having a domain structure of A1-A2-B-A3-C1-C2. Previous transfection studies demonstrated that **factor VIII** is 10-fold less efficiently expressed than the homologous coagulation factor, factor V. The inefficient expression correlated with interaction of the **factor VIII** primary translation product with the protein chaperonin BiP in the lumen of the endoplasmic reticulum. In contrast, factor V was not detected in association with BiP and was secreted efficiently. To **determine** whether specific amino acid sequences within **factor VIII** inhibit secretion, we have studied the secretion of **factor VIII** deletion and **factor VIII**/factor V chimeric proteins upon transient transfection of COS-1 monkey cells. A chimeric **factor VIII** protein that contained the A1- and A2-domains of factor V was secreted with a similar efficiency as wild-type factor V, whereas the **complementary** chimera having the A1- and A2-domains of **factor VIII** was secreted with low efficiency, similar to

wild-type **factor VIII**. These results suggested that sequences within the A1- and A2-domains were responsible for the low secretion efficiency of **factor VIII**. Secretion of A1-domain-deleted **factor VIII** was increased approx. 10-fold compared to wild-type **factor VIII** or A2-domain-deleted **factor VIII**. Expression of the **factor VIII** A1-domain alone did not yield secreted protein, whereas expression of the **factor VIII** A2-domain alone or the factor V A1-domain or A2-domain alone directed synthesis of secreted protein. Secretion of a hybrid in which the carboxyl-terminal 110 amino acids of the A1-domain were replaced by homologous sequences from the factor V A1-domain was also increased 10-fold compared to wild-type **factor VIII**, however, the secreted protein was not functional and the heavy and light chains were not associated. These results localize a 110-amino acid **region** within the A1-domain that inhibits **factor VIII** secretion. This **region** is clustered with multiple short peptide sequences that have potential to bind BiP.

- ST **coagulation factor VIII** domain secretion
chaperonin; **blood coagulation factor VIII** secretion chaperonin; protein BiP **coagulation factor VIII** secretion
- IT Endoplasmic reticulum
(110-amino acid region within A1-domain of **coagulation factor VIII** inhibits secretion from mammalian cells)
- IT **Hemophilia**
(A, 110-amino acid region within A1-domain of **coagulation factor VIII** inhibits secretion from mammalian cells)
- IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GRP78 (glucose-regulated protein, 78,000-mol-weight), 110-amino acid region within A1-domain of **coagulation factor VIII** inhibits secretion from mammalian cells)
- IT Biological transport
(secretion, 110-amino acid region within A1-domain of **coagulation factor VIII** inhibits secretion from mammalian cells)
- IT 9001-24-5, Blood Coagulation factor V 113189-02-9 164641-21-8
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(110-amino acid region within A1-domain of **coagulation factor VIII** inhibits secretion from mammalian cells)

L101 ANSWER 16 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 1994:503079 HCAPLUS

DN 121:103079

ED Entered STN: 03 Sep 1994

TI Chimeric blood coagulation **proteins**

IN Kane, William H.; Ortel, Thomas L.

PA Duke University, USA

SO PCT Int. Appl., 29 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K037-00

ICS C07K013-00; C12N005-10; C12N005-12; C12N015-62; C12N015-79;

G01N033-53

CC 7-2 (Enzymes)

Section cross-reference(s): 1

FAN.CNT 1

PATENT NO.

KIND DATE

APPLICATION NO. DATE

```

-----
PI  WO 9411013      A1  19940526      WO 1993-US10931  19931111 <--
    W: AU, CA, JP
    RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
    AU 9456023      A1  19940608      AU 1994-56023    19931111 <--
    US 5587310      A   19961224      US 1994-273362   19940711 <--
PRAI US 1992-975839      19921113 <--
    WO 1993-US10931      19931111 <--
AB   Chimeric blood coagulation proteins for use in the treatment of
hemophilia and in the mapping of epitopes of the factors are
described. The proteins are either coagulation factor V in
which at least one of the A3, C1 or C2
domain exons is replaced with the homologous exon of coagulation
factor VIII; or coagulation factor
VIII in which at least one of the A3, C1 or
C2 domain exons is replaced with the homologous exon of
coagulation factor V. The construction and expression of genes for
several such analogs is described.
ST   chimeric blood coagulation factor V VIII
IT   Blood analysis
    Immunoassay
        (for antibodies inhibiting blood coagulation factors,
        detection of, fusion proteins of coagulation factors V and
        VIII for)
IT   Antibodies
    RL: BIOL (Biological study)
        (inhibiting blood coagulation factors, detection of, fusion
        proteins of coagulation factors V and VIII for)
IT   Hemophilia
        (treatment of, domain exchange fusion proteins of coagulation
        factors V and VIII for, minimization of immune response in relation to)
IT   Antibodies
    RL: BIOL (Biological study)
        (allo-, inhibiting blood coagulation factors, detection of, fusion
        proteins of coagulation factors V and VIII for)
IT   Gene, animal
    RL: BIOL (Biological study)
        (chimeric, for domain-exchange fusion products of human blood
        coagulation factors V and VIII, expression in animal cell culture of)
IT   9001-24-5D, Blood-coagulation factor V, fusion products with
factor VIII 9001-27-8D, Blood-
coagulation factor VIII, fusion products with
factor V
    RL: BIOL (Biological study)
        (domain exchange in, chimeric gene for, expression in animal; cell
        culture of, for treatment of hemophilia and prophylaxis of
        alloimmunity)

L101 ANSWER 17 OF 19 HCAPLUS  COPYRIGHT 2003 ACS on STN
AN   1988:156310 HCAPLUS
DN   108:156310
ED   Entered STN: 30 Apr 1988
TI   F VIII subunits: purification and antigenic properties
AU   Nordfang, Ole; Ezban, Mirella; Hansen, Jan J.
CS   Nord. Gentofte A/S, Gentofte, Den.
SO   Thrombosis and Haemostasis (1987), 58(4), 1043-8
    CODEN: THHADQ; ISSN: 0340-6245
DT   Journal
LA   English
CC   63-3 (Pharmaceuticals)
    Section cross-reference(s): 13
AB   Factor VIII-light chain (FVIII-LC) and
FVIII-Heavy chain (FVIII-HC) were purified from human

```

plasma using immunosorbents containing monoclonal **antibodies** or human inhibitor **antibodies**. **FVIII-LC** was subsequently isolated in essentially pure state by cation exchange chromatog. The preps. obtained contained 50 ng of **protein** for each unit of **FVIII-LC** antigen (**FVIII-LC:Ag**). Affinity purified **FVIII-LC** and **FVIII-HC** preps. containing <0.3% of the opposite subunit were added in **FVIII:C** inhibition assay of **hemophilia A** inhibitor **antibodies**. **FVIII-C** was able to fully block the inhibitor activity in 6 out of 7 **hemophilia A** plasmas and partially block the inhibitor activity of one plasma. **FVIII-HC** only blocked **FVIII:C** inhibiting **antibodies** from the plasma that was not fully blocked by **FVIII-LC**. **FVIII-LC** can be used for immunotherapy of the patients whose **FVIII:C** inhibiting **antibodies** are directed towards **FVIII-LC**. When **FVIII-LC** was coupled to Sepharose at a concentration of 4800 units of **FVIII-LC:Ag** per mL Sepharose, 0.2 mL of the immunosorbent was able to bind 900 Bethesda units from 100 mL **hemophilia A** inhibitor plasma. This opens the possibility to remove **FVIII** inhibitor **antibodies** from circulation by extracorporeal immunotherapy with **FVIII-LC** coupled to Sepharose.

ST **blood coagulation factor VIII**
purifn; antigenicity **factor VIII**

IT Circulation
(extracorporeal, **factor VIII** inhibitor
antibodies removal in, by immunoadsorption)

IT **Antibodies**
RL: BIOL (Biological study)
(monoclonal, immunosorbents containing, for purification of **blood coagulation factor VIII**)

IT 9012-36-6D, reaction products with **factor VIII**
113189-02-9D, reaction products with Sepharose
RL: BIOL (Biological study)
(**blood coagulation factor VIII**
inhibitor **antibodies** removal by)

IT 113189-02-9P
RL: PREP (Preparation)
(purification and antigenic properties of)

L101 ANSWER 18 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 1986:539598 HCAPLUS

DN 105:139598

ED Entered STN: 18 Oct 1986

TI Preparation for the treatment of **hemophilia A**
inhibitor patients

IN Nordfang, Ole; Rasmussen, Mirella Ezban

PA Nordisk Gentofte, Den.

SO PCT Int. Appl., 32 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K037-02

ICS A61K037-04; A61K035-16; C07K015-06

CC 63-3 (Pharmaceuticals)

Section cross-reference(s): 1, 18

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 8602838	A1	19860522	WO 1985-DK105	19851105 <--
	W: AU, DK, FI, JP, NO, US				
	RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
	CA 1269042	A1	19900515	CA 1985-494555	19851104 <--
	IL 76929	A1	19900726	IL 1985-76929	19851104 <--

AU 8550926	A1	19860603	AU 1985-50926	19851105 <--
AU 599310	B2	19900719		
EP 201574	A1	19861120	EP 1985-905784	19851105 <--
EP 201574	B1	19911127		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
ES 549115	A1	19861201	ES 1985-549115	19851105 <--
JP 62501006	T2	19870423	JP 1985-505194	19851105 <--
AT 69727	E	19911215	AT 1985-905784	19851105 <--
US 4831119	A	19890516	US 1986-881687	19860620 <--
DK 8603180	A	19860704	DK 1986-3180	19860704 <--
DK 165940	B	19930215		
DK 9000418	A	19900216	DK 1990-418	19900216 <--
DK 173863	B1	20020107		
PRAI DK 1984-5253	A	19841105 <--		
EP 1985-905784	A	19851105 <--		
WO 1985-DK105	A	19851105 <--		

AB A composition for the treatment of **hemophilia A** inhibitor patients, those who develop **antibodies** against **Factor VIII:C**, comprises a **protein** or **peptide** having a specific **Factor VIII:CAg** activity of ≥ 0.5 U/mg **protein** characterized by a ratio of **Factor VIII:CAg** to **Factor VIII:C** procoagulant activities of 5-10:1. A fragment of **Factor VIII:C**, which displays a doublet of a mol. weight of 80/77 kD in electrophoresis, is the reactive **hemophilia A** inhibitor **antibodies** and has **VIII:CAg** activity. This fragment and more low-mol.-weight fragments of **Factor VIII:C** are capable of neutralizing the coagulation inhibiting effect of all tested **antibodies**. Such fragments can therefore be used as active component in preps. for providing immunotolerance towards **Factor VIII:C** in high-dose treatment of inhibitor patients. The **peptides** are useful as an immunosorbent in specific extracorporeal adsorption treatment of inhibitor patients. The inhibitor reactive **peptides** can be recovered from plasma fractions by affinity chromatog., hydrophobic interaction chromatog. or cation exchange or they may be produced biosynthetically and recovered in a similar manner. **IgG** was coupled to Sepharose 4B activated with CNBr, blocked with glycine, washed with buffers, and the gel incubated with AHF. The gel was washed on a column with buffer and eluted with the buffer to give an eluate containing **VIII:CAg**.

ST **hemophilia A** inhibitor factor **VIII:C**

IT **Hemophilia**
(A, inhibitor patients, treatment of, with blood coagulation factor **VIII:CAg** and factor **VIII:C**)

IT **Immunoglobulins**
RL: PREP (Preparation)
(G, blood coagulation factor **VIII:CAg** preparation of, for treatment of **hemophilia A** inhibitor patients)

IT **9001-27-8P**
RL: PREP (Preparation)
(clotting antigen and blood coagulant activity of, preparation and treatment of **hemophilia A** inhibitor patients with)

L101 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
 AN 1979:454297 HCAPLUS
 DN 91:54297
 ED Entered STN: 12 May 1984
 TI Rapid isolation and purification of **antibody** to **Factor VIII** by **protein A**
 AU Lee, Helen; Tucker, Derek; Allain, J. P.
 CS Oxford Haemophilia Cent., Churchill Hosp., Oxford, UK

SO Thrombosis Research (1979), 14(6), 925-30
CODEN: THBRAA; ISSN: 0049-3848

DT Journal

LA English

CC 15-1 (Immunochemistry)

AB A simple and reproducible method was developed for rapidly isolating and purifying **antibodies to blood-coagulation Factor VIII** from the plasma of both **hemophilic** and nonhemophilic patients. The 1-step separation of these **Igs** makes use of the high affinity binding of **protein A** with the Fc region of the human IgG1, IgG2, and **IgG4** subclasses but not with the IgG3 subclass. Small **protein A-Sepharose CL-4B** gel columns were used to isolate the **IgG** subclasses which contain the anti-**Factor VIII** activity from as little as 0.5 mL of plasma. The yield of the **antibody** was 70-80%. When the purification procedure was combined with a solid phase agarose gel assay for **antibody to factor VIII**, a large number of samples could be tested and only small amts. of patient's plasma were required. The plasma of a patient with **antibody** to factor V was also fractionated by **protein A** with similar results.

ST **protein A factor VIII antibody;**
staphylococcal protein A antibody factor
VIII; coagulation factor VIII
antibody isolation

IT' Staphylococcus aureus
(**protein A** of, in **blood-coagulation**
factor VIII antibody isolation and purification)

IT **Antibodies**
RL: BIOL (Biological study)
(to **blood-coagulation factor VIII**
, chromatog. isolation and purification of, staphylococcal **protein**
A in)

IT **Proteins**
RL: BIOL (Biological study)
(A, of Staphylococcus, in **blood-coagulation**
factor VIII antibody isolation and purification)

IT 9001-24-5 9001-27-8
RL: BIOL (Biological study)
(**antibodies** to, chromatog. isolation and purification of,
staphylococcal **protein A** in)

=>